

REMARKS/ARGUMENTS

The Office Action dated March 18, 2009, rejected all pending claims, i.e., claims 1-3 and 5-16. Claim 13 has been amended in this response to add the punctuation suggested by the Examiner.

With respect to the double-patenting rejection, Applicants submit a terminal disclaimer over now-issued U.S. Patent No. 7,563,466. Just as those claims were patentable, so too are the pending claims. Withdrawal of the double-patenting rejection is earnestly solicited.

Applicants appreciate the Examiner's diligence in searching and examining the pending claims. Applicants nevertheless note that the presently pending obviousness rejection is fundamentally similar to the previous three obviousness rejections, all of which alleged obviousness based on combinations of different references that allegedly individually disclosed disparate portions of the claimed subject matter:

- The Official Action dated February 13, 2007 rejected the claims as allegedly obvious over U.S. Patent App. Pub. 2003/0003140 A1 to Domb et al. (Domb), U.S. Patent No. 5,543,154 to Rork et al. (Rork), U.S. Patent No. 5,780,046 to Humber et al. (Humber), and/or PCT Publication WO 02/094300 A1 to Levine et al. (Levine '300).
- The Official Action dated November 13, 2007 rejected all claims as allegedly obvious over U.S. Pat. App. Pub. No. 2002/0136755 to Tyrrell et al. (Tyrrell) in light of U.S. Pat. No. 4,742,046 to Bliah (Bliah), Rork, and/or Humber.
- The Final Office Action dated June 18, 2008, rejected all claims as allegedly obvious over PCT Pub. No. WO 99/20289 to Oppenheim et al. (Oppenheim), U.S. Patent No. 5,639,473 to Grinstaff et al. (Grinstaff), Brinkhaus et al, Phytomedicine 7, 427-448 (2000) (Brinkhaus), U.S. Patent Pub. No. 2002/0165169 A1 to Kim et al. (Kim), and/or U.S. Patent No. 5,863,553 to Britton et al. (Britton).

Applicants certainly appreciate the withdrawal of all previous rejections, but Applicants stress that if the pending subject matter is allowable over the cited prior art, the Patent Office's

response ought include a Notice of Allowance, not another similar rejection based on yet another set of references.

In the present Office Action, all pending claims were rejected as allegedly unpatentable under 35 U.S.C. § 103 over U.S. Patent No. 6,217,918 to Mathiowitz et al. (Mathiowitz); an internet “publication” titled “1001herbs”; an internet “publication” titled “Holistic-Online”; and Ceschel et al., Drug Delivery (2001) (Ceschel).

As an initial matter, Applicants note the two internet “publications” bear a retrieval dates well after the priority (and filing) date of this application. According to MPEP § 2128 (with emphasis added): “Prior art disclosures on the Internet or on an on-line database are considered to be publicly available as of the date the item was publicly posted. Absent evidence of the date that the disclosure was publicly posted, if the publication itself does not include a publication date (or retrieval date), it cannot be relied upon as prior art under 35 U.S.C. 102(a) or (b).” Accordingly, the Patent Office has not demonstrated that these “publications” were indeed publicly available prior art. Merely posting a copyright notice is insufficient to show the precise *content*, if any, of the pages at any time prior to the retrieval date. *Cf. Paris Glove of Canada Ltd. v. SBC/Sporto Corp.*, 84 USPQ2d 1856, 1858-59 (TTAB 2007) (holding that even material obtained from the “Wayback Machine” is unreliable). Regardless, the cited internet publications do not render the pending claimed subject matter unpatentable, either alone or in combination with the other cited references.

As fully defined in the pending claims, the invention relates to a therapeutic composition having the following features:

(1) The active ingredient is a mixture comprising extracts of three specific herbs (extracts of the plants *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea*).

(2) The composition is in a solid form and is mucoadhesive, and therefore adheres to the mucosal tissue (in order to locally treat inflamed mucosa).

(3) The excipients combined in the composition together with the aforementioned herbs are the following: an adhesive polymer of acrylic acid, polyvinylpyrrolidone and also a bulk ingredient (lactose).

An important aspect of the presently claimed subject matter is that a mixture of extracts obtained from the plants *Sambucus nigra*, *Centella asiatica* and *Echinacea purpurea* is incorporated in a solid mucoadhesive composition together with a polymer of acrylic acid and polyvinylpyrrolidone, with the benefit of attaining a dosage form having enhanced bioadhesiveness. The improved bioadhesiveness unexpectedly attained by the solid composition of the invention is illustrated in the working examples in the specification. The experimental results given in the description indicate a considerable increase in the adhesiveness of the composition, following the addition of the three herbs mixture. (See, e.g., Specification at 10-14.) The mucoadhesive composition of the claimed invention may therefore be placed onto the mucosa, to effectively deliver the herbs and accomplish the local treatment. It is noted that the mixture of herbs constitutes the active ingredient to be delivered by solid dosage form and to be absorbed by the mucosa, and at the same time, the herbal mixture contributes appreciably to the overall adhesiveness of the solid dosage form. A preferred dosage form provided by the invention is the tablet of claim 2, with its specific structural features.

The Office Action rejected the claims on the grounds of obviousness over several combinations of prior art citations, and it appears that the primary reference is Mathiowitz.

Mathiowitz is concerned with the enhancement of the bioadhesiveness of polymeric microcapsules. To this end, the patent suggests the modification of the microcapsules through

the covalent binding of lectin onto their surface. At the outset it should be pointed out that Mathiowitz contains no disclosure of *Centella* or *Echinacea* and certainly no disclosure of a mixture comprising the three herbs as employed according to the present invention. Furthermore, it is respectfully submitted that Mathiowitz also does not teach the combination of an adhesive polymer of acrylic acid, polyvinylpyrrolidone and *Sambucus nigra*.

Regarding the polymers which can be used for making the microcapsules, it is noted that Mathiowitz provides a large list of suitable polymers on column 7 and 8. Although polyacrylic acid and polyvinylpyrrolidone are mentioned in the list, there is no enabled disclosure of a combination comprising both these polymers, and Mathiowitz's working examples clearly give preference to *other* types of polymers.

Regarding the *Sambucus nigra*, Mathiowitz only briefly mentions said herb as a possible source of lectin. In Column 11 of the patent, a large list of sources for lectin is provided, one of which is identified *Sambucus nigra*. More specifically, the language of the paragraph is as follows (emphasis added):

Lectins that can be covalently attached to microspheres to render them target specific to the mucin and mucosal cell layer could be used as bioadhesives. Useful lectin ligands include lectins isolated from: *Abrus precatorius*, *Agaricus bisporus*, *Anguilla anguilla*, *Arachis hypogaea*, *Pandeiraea simplicifolia*, *Bauhinia purpurea*, *Caragan arobrescens*, *Cicer arietinum*, *Codium fragile*, *Datura stramonium*, *Dolichos biflorus*, *Erythrina corallodendron*, *Erythrina cristagalli*, *Euonymus europaeus*, *Glycine max*, *Helix aspersa*, *Helix pomatia*, *Lathyrus odoratus*, *Lens culinaris*, *Limulus polyphemus*, *Lysopersicon esculentum*, *Maclura pomifera*, *Momordica charantia*, *Mycoplasma gallisepticum*, *Naja mocambique*, as well as the lectins *Concanavalin A*, *Succinyl-Concanavalin A*, *Triticum vulgaris*, *Ulex europaeus I, II and III*, *Sambucus nigra*, *Maackia amurensis*, *Limax fluvius*, *Homarus americanus*, *Cancer antennarius*, and *Lotus tetragonolobus*.

Of note, there is no teaching in Mathiowitz that the lectins from *Sambucus nigra* are to be preferred over any of the other lectins mentioned in the list. Furthermore, to be useful the lectins (which are carbohydrate-binding proteins and in the case of *Sambucus* are found only in extracts of the bark of the tree) would need to be covalently linked to the microsphere surface disclosed in Mathiowitz. It follows that the *Sambucus nigra* lectin incorporated in the composition of Mathiowitz is necessarily in a covalently bound form.

The *Sambucus nigra* lectin is not an active ingredient to be delivered by the composition of Mathiowitz. Instead the reference provides a separate list of active materials that can be incorporated into the composition (see column 14). Moreover, there is no indication in Mathiowitz that the microspheres are suitable for delivering plant materials. All a person of ordinary skill in the art would glean from Mathiowitz is that if *Sambucus nigra* lectin is to be used, then it needs to be covalently linked to the polymeric microsphere.

To summarize some of the deficiencies of Mathiowitz: the total number of possible combinations of polymers and lectin sources disclosed is undoubtedly a very large number; the reference gives no preference to making microcapsules made of polyacrylic acid and polyvinylpyrrolidone combined with *Sambucus nigra* lectin. Even if there were an express suggestion in Mathiowitz to combine *Sambucus nigra* lectin with these two particular polymers, the combination would still require some chemical modification in order to allow the covalent binding between the chemical species. It is not at all clear how polyacrylic acid and polyvinylpyrrolidone can be combined to form a mixed microcapsule, and how the covalent binding of the *Sambucus nigra* lectin to the polyvinylpyrrolidone would alter the chemical structure of the latter. It is absolutely clear, however, that a non-covalent association of *Sambucus nigra* lectin with the microspheres is not taught by Mathiowitz. According to the

presently claimed subject matter, the plant extracts are active ingredients and are, therefore, incorporated in a non-covalently bound form.

In order to cure some of the deficiencies noted above with respect to US 6,217,908, the examiner relies on several secondary prior art references: internet publications entitled "1001 herbs" and "Holistic-Online" and Ceschel.

Regarding the combination of Mathiowitz with the internet-based citations, Applicants wish to point out that it appears that "1001 Herbs" and "Holistic online" merely discuss the medicinal properties of the herbs. In order to justify the combination of the three herbs with the drug delivery system of Mathiowitz, the Patent Office appears to take the position on pages 5-6 that:

The drug delivery of Mathiowitz et al. can be used to deliver the 1001 herbs taught *Echinacea purpurea* ...and Holistic-online taught *Centella Asiatica*... Thus, an artisan of ordinary skill would reasonably expect that ingredient that can boost immune system could be used... This reasonable expectation of success would motivate the artisan to use *Sambucus nigra*, *Centella Asiatica* and *Echinacea purpurea* as the muco-adhesive drug in the composition. Thus, using *Sambucus nigra*, *Centella Asiatica* and *Echinacea purpurea* as the muco-adhesive drug is considered an obvious modification of the references.

However, the medicinal properties of *Echinacea purpurea* and *Centella Asiatica* reported separately in "1001 Herbs" and "Holistic online", respectively, are completely unrelated to the formulation of the three herbs in a solid dosage form exhibiting enhanced mucoadhesion. The question to be considered is whether the secondary references cited fairly provide the reader with sufficient information to formulate *Echinacea purpurea*, *Centella Asiatica* and *Sambucus nigra* together with a polymer of acrylic acid and polyvinylpyrrolidone, to provide a mucoadhesive dosage form, with an expectation that a greater adhesion is attained by the addition of said herbs.

The references cited are silent regarding the delivery of *Echinacea purpurea* and *Centella Asiatica* in a mucoadhesive composition and their capacity to increase the adhesiveness of a solid dosage form. The fact that the herbs possess therapeutic properties pertinent to various ailments in no way suggests that they would enhance adhesion to mucosal surfaces. Thus, there is absolutely no prior teaching based on the medicinal properties of *Echinacea* and *Centella* described in the references cited that would lead one to expect that the combination of *Sambucus*, *Centella*, and *Echinacea*, when added to adhesive polymers, (polymer of acrylic acid, polyvinylpyrrolidone), enhances adhesion of the resulting composition, to afford a solid dosage form which is mucoadhesive.

Regarding the combination of Mathiowitz with Ceschel, the Patent Office appears to take the position on page 6 of the Office Action that:

Thus, it would be obvious to add lactose into mucoadhesive formulation, such as that taught by Ceschel et al. An artisan of ordinary skill would clearly expect that the bioadhesive tablets taught by Ceschel et al. would function successfully to administer the bioadhesive microcapsules taught by Mathiowitz et al. This reasonable expectation of success would motivate the artisan to modify Mathiowitz et al to include lactose as an effective means to administer the bioadhesive formulation.

Applicants respectfully disagree. It should be pointed out that Mathiowitz is concerned with polymeric microspheres. And column 14, lines 43-48, explains that the microspheres are administered in suspension or in ointment to the mucosal membranes. Thus, the microspheres of Mathiowitz are not intended to be used to form a tablet. There is no indication that the microspheres can be processed to form tablets (e.g., that the microspheres are flowable; that the microspheres can be wet granulated and compressed).

Finally, it is respectfully submitted that the Office Action did not provide arguments against the inventiveness of claim 2, which is directed to a tablet having specific structure (adhesive face and a coated, non-adhesive face). Page 4 of the Office Action states: “The non-adhesive side would be intrinsically taught because the inside of the shell would be in contact with the dispersing agent; thus, the dispersing agent would be the non adhesive side.”

But the passage cited above is completely unrelated to the publications discussed in the Office Action and appears to have been erroneously copied from the previous Office Action. Therefore, Applicants find nothing in the Office Action which addresses the limitations of claim 2.

It is important to note that the Patent Office’s obviousness rejection again requires picking and choosing selected, disjointed disclosures of particular references (albeit new references when compared with the previous official actions) and building a mosaic to form the claimed subject matter. There is no legally sufficient reason that one skilled in the art would have collected the seven asserted references and derived the claimed subject matter through emphasizing certain portions of the references while ignoring others. For example, the Supreme Court instructed in *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809 (1986) that “in addressing the question of obviousness a judge must not pick and choose isolated elements from the prior art and combine them so as to yield the invention in question if such a combination would not have been obvious at the time of the invention.” 475 U.S. at 810. Just as a judge may not pick and choose isolated teachings, neither may the Patent Office.

All claims are in good condition for allowance. If any small matter remains outstanding (e.g., that may be resolved with an Examiner’s Amendment), the Examiner is encouraged to

telephone Applicants' representative. Prompt reconsideration and allowance of this application is requested.

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140.

Respectfully submitted,

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